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Insulin and Endometrial Cancer

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Elevated insulin levels may explain part of the increased risk of endometrial cancer observed in obese postmenopausal women. Circulating sex hormones and fasting C-peptide levels were measured in sera obtained from 165 postmenopausal endometrial cancer cases accrued between June 1, 1987, and May 15, 1990, from hospitals in Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina, and 180 community and hysterectomy controls. Women with a personal history of diabetes were excluded. Among controls, C-peptide was positively correlated with body mass index (BMI) ($r = 0.44$), waist-to-thigh circumference ratio ($r = 0.24$), estrone ($r = 0.18$), and estradiol ($r = 0.28$) (albumin-bound ($r = 0.45$), and free ($r = 0.37$)) and negatively correlated with sex hormone-binding globulin ($r = -0.48$). In age-adjusted analyses, the odds ratios and 95% confidence intervals for tertiles of C-peptide and endometrial cancer were, from lowest to highest: 1.0 (reference), 0.78 (95% confidence interval (CI) 0.43–1.4), and 2.2 (95% CI 1.3–3.7). Further adjustment for BMI substantially attenuated the odds ratios for the highest tertile of C-peptide (odds ratio = 1.2, 95% CI 0.63–2.1), and adjustment for body mass index and other risk factors for endometrial cancer eliminated the association (odds ratio = 1.0, 95% CI 0.55–2.0). In contrast, adjustment for C-peptide had little influence on the magnitude of the positive associations between body mass index (odds ratio for highest vs. lowest tertile, without and with adjustment for C-peptide = 4.1 (95% CI 2.3–7.5) and 3.7 (95% CI 1.9–7.1), respectively) or several steroid hormones and endometrial cancer. These data are not consistent with the hypothesis that the effect of obesity on endometrial cancer risk is mediated through high insulin levels. *Am J Epidemiol* 1997;146:476–82.

body mass index; C-peptide; endometrial neoplasms; hyperinsulinism; sex hormones

The identified risk factors for endometrial cancer are consistent with a hormonal etiology. The effects of reproductive, anthropometric, and medical risk factors are hypothesized to be mediated through a single mechanism, namely, the influence of relatively high levels of estrogen on the endometrium, particularly when unopposed by progesterone (1). Obesity, an especially strong risk factor for endometrial cancer, is postulated to increase risk in postmenopausal women through extragonadal conversion of androstenedione to estrogen in adipose tissue (2–4). Despite the wide acceptance of this mechanism, few studies have evaluated endometrial cancer risk in relation to adiposity and sex hormones simultaneously (5, 6). In fact, recent data (5) cast doubt on whether estrogens alone can explain the obesity effect and may indicate the involvement of other mechanisms.

Obesity is associated with a constellation of metabolic alterations (7), including elevations in the growth factor insulin (8, 9). Elevated insulin levels also are associated with such endometrial cancer risk factors as upper-body or central adiposity (10), polycystic ovarian syndrome, physical inactivity (11–13), and a diet high in saturated fat (11). Moreover, several small studies have reported positive associations of fasting and postprandial insulin levels with endometrial cancer in postmenopausal women (14, 15).

The independent relations of adiposity and blood hormone levels with endometrial cancer risk in this large multicenter case-control study have been reported previously (5). In this paper, we evaluated the hypothesis that insulin, as measured by C-peptide levels, mediates the effects of obesity and upper-body adiposity on risk. In addition, we assessed whether insulin influenced the relations between several steroid hormones and sex hormone-binding globulin (SHBG) with risk of endometrial cancer.

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Abbreviations: BMI, body mass index; CI, confidence interval; HCFA, Health Care Financing Administration; OR, odds ratio; RDD, random digit dialing; SD, standard deviation; SHBG, sex hormone-binding globulin; WTR, waist-to-thigh ratio.

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MATERIALS AND METHODS

A detailed description of case and control selection and other study methods is presented elsewhere (16). Briefly, cases were accrued during the period June 1, 1987 to May 15, 1990, from seven hospitals in five geographic regions: Chicago, Illinois; Hershey, Pennsylvania; Irvine and Long Beach, California; Minneapolis, Minnesota; and Winston-Salem, North Carolina. Eligible for study were 498 women with newly diagnosed, pathologically confirmed endometrial cancer who were between ages 20 and 74 years, resided in defined geographic catchment areas, and had not received previous treatment for their cancer. Two types of controls, community and hospital-based, were matched to cases according to age (5-year categories) and race (white, black, other). For community controls aged 20–64 years, random digit dialing (RDD) procedures were used to select women with telephone exchanges similar to those of cases. Older controls were selected using information on age, race, and broad category of zip code provided by the Health Care Financing Administration (HCFA). Hysterectomy status was obtained by a short telephone screener administered to all potential controls. Women without an intact uterus were replaced with another eligible subject. A second, smaller control group consisting of women who had hysterectomies for benign conditions at the seven referral hospitals was added to ensure some comparability in women referred to a specialized hospital for hysterectomy. In addition, hysterectomy controls were included to increase the response rates to the interview and blood components of the study. Primary diagnoses for the postmenopausal hysterectomy control subjects were genital prolapse (67.2 percent), stress incontinence (8.1 percent), ovarian neoplasm (6.5 percent), endometrial cystic hyperplasia (6.5 percent), uterine leiomyoma (4.8 percent), and other disorders (6.9 percent), including endometriosis and other noninflammatory disorders of the ovaries or fallopian tubes. The matching criteria, especially for age, had to be relaxed occasionally for both control groups. There were a total of 730 eligible hysterectomy (n = 253), RDD (n = 304), and HCFA (n = 173) controls.

Trained interviewers administered a standardized interview at the subjects' homes, eliciting information on demographic and various lifestyle factors, reproductive history, use of exogenous hormones, and body measurements. Women were classified as postmenopausal if they reported no menses in the 6 months prior to the interview or blood collection. Waist and thigh circumferences were measured to the nearest 0.1 cm with a spring-loaded fiberglass tape by interviewers who received standardized training (17). The ratio of waist to thigh circumference (WTR) was formed as a measure of central adiposity. Self-reported values for weight and height were used to calculate body mass index (BMI) (weight (kg)/height $(m)^2$).

Of the 498 eligible cases, 434 (87.1 percent) completed interviews. Cases with sarcomas and their matched controls were removed from the analysis because of the distinct epidemiologic characteristics of sarcomas (18). Of the 434 interviewed cases, 325 agreed to donate blood samples. Of the 730 eligible controls, 206 of the hysterectomy controls, 232 of the RDD controls, and 81 of the HCFA controls completed interviews. Of the 519 interviewed controls, 139 of the hysterectomy controls and 217 of the community controls agreed to donate blood samples. Analyses were restricted to postmenopausal women who completed an interview and donated blood (246 cases, 78 hysterectomy controls, and 160 community controls). Thirty-eight cases and 29 controls (14 hysterectomy and 15 community) who had used exogenous estrogens or oral contraceptives within 6 months of the interview were excluded. In addition, 35 cases and 17 controls (five hysterectomy and 12 community) who reported a personal history of diabetes were excluded from the analytic study. C-peptide values were not determined for eight cases and 11 controls (three hysterectomy and eight community) owing to insufficient specimen remaining after the initial hormone analyses, and one community control with a log-transformed value for C-peptide approximately five standard deviations from the mean was excluded from the analysis. In total, 345 postmenopausal women (165 cases, 56 hysterectomy controls, and 124 community controls) with values for both the sex hormones and C-peptide were included in the analysis.

Fasting blood samples were collected from cases and hysterectomy controls prior to surgery and usually within 1 month of the interview for community controls. Serum was stored at −85°C for up to 7 years. Serum hormone levels, with the exception of C-peptide, were determined at Nichols Institute, Inc. (San Juan Capistrano, California). The measurement and reproducibility of the sex hormones estrone, total estradiol, free estradiol, albumin-bound estradiol, and androstenedione and of SHBG have been described in detail elsewhere (19). Coefficients of variation ranged from 10.8 for androstenedione to 18.2 for free estradiol. C-peptide levels were determined at American Medical Laboratories, Inc. (Chantilly, Virginia) and were measured in serum by radioimmunoassay with guinea pig antihuman C-peptide antiserum. All subjects' samples were tested twice and averaged. When the test and retest differed by a predetermined amount, a second set of tests was performed and the overall

average of both sets was calculated. Multiple blind quality surveillance blood samples that were aliquots from a low and high C-peptide pool (from two women) were inserted into all batches with the blood samples from subjects to monitor quality control. Repeated analyses of these pools in the same and different batches revealed overall coefficients of variation of 14.3 percent for the low C-peptide pool and 10 percent for the high pool.

Pearson correlation coefficients were calculated between C-peptide and the anthropometric indices, sex hormone measures, and SHBG by using continuous variables, for cases and controls separately (Spearman correlations gave similar results). Quartiles of BMI and WTR were categorized based on their distributions in pre- and postmenopausal controls, and tertiles of C-peptide and the sex hormones were based on their distributions in postmenopausal controls. In general, the two control groups were similar with respect to risk factors for endometrial cancer demonstrated in this study (table 1), including C-peptide levels, so the control groups were combined to increase statistical power. Odds ratios and 95 percent confidence intervals were calculated as estimators of relative risk using unconditional logistic regression (20).

RESULTS

The major risk factors identified in these data, after adjustment for each other, included history of use of menopausal estrogens (odds ratio (OR)$_{\geq 4 \text{ vs. } <4 \text{ months use}}$ = 2.7, 95 percent confidence interval (CI) 1.2–6.1); history of use of oral contraceptives (OR = 0.37, 95 percent CI 0.18–0.77); serum cholesterol level (OR$_{\text{high vs. low (dichotomized at median)}}$ = 0.52, 95 percent CI 0.31–0.85); BMI (OR$_{\text{highest quartile vs. lowest three quartiles}}$ = 4.3, 95 percent CI 2.5–7.3); nulliparity (OR$_{\text{nulliparous vs. parous}}$ = 1.2, 95 percent CI 0.59–2.6); age at menarche (OR$_{<13 \text{ vs. } \geq 13 \text{ years}}$ = 2.0, 95 percent CI 1.2–3.2); and nonrecreational physical activity (OR$_{\text{highest tertile vs. lowest tertile}}$ = 0.34, 95 percent CI 0.18–0.65).

The mean age at interview was 62.8 years for the cases, 62.1 years for the hysterectomy controls, and 61.9 years for the community controls. The majority of subjects were white (90.4 percent of the cases, 91.1 percent of the hysterectomy controls, and 95.9 percent of the community controls). Mean BMI was 30.9 (standard deviation (SD) = 9.6, range = 17.9–78.6) for the cases, 26.1 (SD = 6.1, range = 14.0–49.8) for the community controls, and 25.8 (SD = 5.6, range = 18.0–45.2) for the hysterectomy controls. Mean C-peptide was 2.51 (SD = 1.36, range = 0.6–9.6) for the cases, 2.04 (SD = 1.05, range = 0.6–7.0) for the community controls, and 1.96 (SD = 0.99, range = 0.6–5.1) for the hysterectomy controls.

TABLE 1. Distribution of selected risk factors for endometrial cancer by case and control groups, United States, 1987–1990*

Risk factor	Cases (%) (*n* = 165)	Community controls (%) (*n* = 124)	Hysterectomy controls (%) (*n* = 56)
BMI† (quartiles)			
<22.5	18.2	26.6	32.1
22.5–25.9	14.6	23.4	25.0
26.0–28.2	13.3	27.4	23.2
>28.2	53.3	22.6	19.6
WTR† (quartiles)			
<1.62	9.7	19.4	12.5
1.62–1.78	20.6	29.8	28.6
1.79–2.0	26.7	24.2	21.4
>2.0	37.0	25.8	32.1
Parity			
Nulliparous	15.2	9.7	12.5
Parous	84.2	90.3	87.5
Age at menarche (years)			
≤13	76.4	66.1	62.5
>13	22.4	32.3	37.5
Oral contraceptive use			
Never	90.3	77.4	80.4
Ever	9.7	22.6	19.6
Estrogen use (months)			
<4	84.2	91.1	91.1
≥4	15.2	8.9	8.9
Nonrecreational activity (tertiles)			
Low	48.5	33.9	39.3
Medium	30.9	33.0	28.6
High	19.4	33.0	32.1
Blood cholesterol level (mg/dl)			
≤226	47.9	34.7	30.3
>226	47.9	62.1	69.7

* Percentages do not always add to 100 because of missing values.

† BMI, body mass index (weight (kg)/height (m)^2); WTR, waist-to-thigh ratio.

C-peptide was not correlated with age or height but was highly and positively correlated with BMI and weight and, to a lesser degree, WTR (table 2). The correlation between C-peptide and WTR appeared to be independent of BMI. C-peptide was positively correlated with most of the hormones except androstenedione and was negatively correlated with SHBG. Adjustment for BMI eliminated the correlations between C-peptide and most of the hormones except

TABLE 2. Pearson correlation coefficients between C-peptide and age, anthropometric variables, sex hormones, and SHBG* among postmenopausal controls (n = 180), United States, 1987–1990

	Unadjusted	BMI*-adjusted
Age	0.04	0.10
BMI*	0.44	
Weight	0.40	
Height	−0.11	−0.04
WTR*	0.24	0.28
E1*	0.18	−0.01
Total E2*	0.28	0.01
Free E2	0.37	0.10
Albumin-bound E2	0.45	0.22
Androstenedione	−0.0005	−0.04
SHBG	−0.48	−0.36

* SHBG, sex hormone-binding globulin; BMI, body mass index (weight (kg)/height (m)^2); WTR, waist-to-thigh ratio; E1, estrone; E2, estradiol.

albumin-bound total estradiol and SHBG, which were attenuated.

The age-adjusted odds ratio of endometrial cancer for the highest tertile of C-peptide compared with the lowest tertile was elevated and statistically significant, although there was no evidence of a trend (table 3). Adjustment for BMI strongly attenuated the elevated risk associated with high C-peptide levels, although adjustment for WTR had little effect. Further adjustment for factors associated with endometrial cancer in addition to BMI entirely eliminated the association for the highest tertile of C-peptide (table 3).

The elevated odds ratio observed for high C-peptide levels was generally attenuated with individual adjustment for the sex hormones, although the odds ratio was unchanged with adjustment for androstenedione (results not shown). Further adjustment for BMI, in addition to the individual hormones, resulted in estimates similar to those obtained with adjustment for age and BMI only (results not shown), suggesting that any influence of the hormones on the association of C-peptide with endometrial cancer was due to their correlation with BMI.

Table 4 presents data on the influence of C-peptide on the associations for BMI and WTR. BMI was positively associated with endometrial cancer risk, although the effect was limited to the heaviest women. Adjustment for C-peptide, in addition to age, slightly attenuated the odds ratio for BMI. WTR also was positively associated with risk. Adjustment for BMI attenuated the risk associated with the highest level of WTR, but further adjustment for C-peptide had no effect.

As reported previously (5), each of the sex hormones was positively associated with endometrial cancer risk, with the exception of SHBG, which demonstrated an inverse relation. Adjustment for BMI diminished the associations for the hormones; however, the relations for androstenedione and SHBG remained. The results were unchanged with further adjustment for C-peptide (results not shown).

Several further analyses were performed to address possible sources of bias. To examine the possibility that subjects had not fasted before their blood was drawn, analyses for C-peptide were repeated among women with serum triglyceride levels of less than 200 mg/dl. The tertile results were similar to those obtained overall (age- and BMI-adjusted OR for tertiles = 1.0 (referent), 0.66, and 1.3). Since the relation of adiposity to risk was limited to the heaviest women, we assessed the association for C-peptide among women with a BMI of less than 28.2 kg/m^2. The results were similar to the overall age-and BMI-adjusted results (age-adjusted OR for tertiles = 1.0 (referent), 0.54, and 1.2). Finally, when cases were compared with the community controls only, the age- and BMI-adjusted OR was 1.0 (95 percent CI 0.52–1.9) for the highest versus the lowest tertile of C-

TABLE 3. Odds ratios and 95% confidence intervals for C-peptide and endometrial cancer among postmenopausal women, United States, 1987–1990

Variables adjusted for*	Tertiles of C-peptide				
	Low (<1.6 ng/ml) (64 controls, 44 cases) Odds ratio	Medium (1.6–<2.2 ng/ml) (57 controls, 31 cases)		High (≥2.2 ng/ml) (59 controls, 90 cases)	
		Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Age	1.0	0.78	0.43–1.4	2.2	1.3–3.7
Age, BMI	1.0	0.64	0.35–1.2	1.2	0.63–2.1
Age, WTR	1.0	0.76	0.41–1.4	2.0	1.2–3.5
Multivariate	1.0	0.63	0.32–1.2	1.0	0.55–2.0

* Age was adjusted for by using continuous values, and body mass index (BMI) and waist-to-thigh ratio (WTR) were adjusted for by using indicator variables. Included in the multivariate model were age, BMI, WTR, nulliparity, age at menarche, oral contraceptive use, menopausal estrogen, nonrecreational physical activity, and quartiles of serum cholesterol.

TABLE 4. Odds ratios and 95% confidence intervals for endometrial cancer associated with body mass index and waist-to-thigh ratio, United States, 1987–1990*

	% of controls (n = 180)	% of cases (n = 165)	Age-adjusted odds ratio	95% confidence interval	Odds ratio adjusted for age and BMI	95% confidence interval	Odds ratio adjusted for age, BMI, and C-peptide†	95% confidence interval
BMI (quartiles)								
<22.5	28.3	18.2	1.0				1.0	
22.5–25.9	23.9	14.5	1.0	0.51–2.0			1.0	0.51–2.0
26.0–28.2	26.1	13.3	0.83	0.42–1.7			0.81	0.40–1.6
>28.2	21.7	53.3	4.1	2.3–7.5			3.7	1.9–7.1
WTR (quartiles)								
<1.62	17.2	9.7	1.0		1.0		1.0	
1.62–1.78	29.4	20.6	1.2	0.59–2.6	1.6	0.71–3.5	1.6	0.73–3.7
1.79–2.0	23.3	26.7	2.0	0.96–4.2	2.0	0.92–4.5	2.1	0.93–4.7
>2.0	27.8	37.0	2.3	1.1–4.7	1.6	0.74–3.5	1.7	0.75–3.7

* There is one missing value for body mass index (BMI) (weignt (kg)/height (m)^2), and there are 14 missing values for waist-to-thigh ratio (WTR). Age was adjusted for by using continuous values, and body mass index and C-peptide were adjusted for by using indicator variables.
† BMI is adjusted for age and C-peptide.

peptide, and when cases were compared with hysterectomy controls, the comparable OR was 1.5 (95 percent CI 0.67–3.6).

DISCUSSION

While estrogens are strongly implicated in the etiology of endometrial cancer, recent data have raised some question about whether they alone can explain the identified risk factors for this disease (5). In this study, we evaluated the hypothesis that insulin is associated with endometrial cancer risk, either independently of adiposity or by mediating its effect. Although we observed an increased risk of endometrial cancer among women with high levels of C-peptide, the association was eliminated after adjustment for BMI. In contrast, adjustment for C-peptide did not influence the positive association between BMI and endometrial cancer risk and had little impact on the associations for several sex hormone measures and risk after adjustment for BMI.

C-peptide levels are regarded as a valid marker of pancreatic insulin secretion (21). Unlike insulin, which shows considerable variation in hepatic clearance, 85–90 percent of C-peptide reaches the peripheral circulation. Explicit information on insulin resistance was unavailable in this study; however, the positive correlations of C-peptide with BMI and WTR are supportive of high C-peptide levels, reflecting insulin resistance and possibly hyperinsulinemia. Further, we found an inverse association between SHBG and C-peptide, as has been noted for insulin (22).

To the extent that serum C-peptide reflects circulating insulin levels, our findings are in disagreement with previous studies demonstrating a positive relation between insulin and endometrial cancer risk (13, 14). Higher fasting and postchallenge insulin, but not glucose levels, were found in 10 postmenopausal endometrial cancer cases compared with 10 noncases matched on age, percent of ideal body weight, and years since menopause (13). In this study, despite the use of weight as a matching criterion, mean percent of ideal body weight was higher in cases than in controls. In another study using similar matching criteria (14), fasting and postchallenge glucose and insulin levels were higher in 32 cases than in 18 noncases, although insulin sensitivity, as represented by the ratio of fasting glucose to insulin, did not differ. Cases had greater glucose intolerance in an earlier and larger clinical laboratory investigation of endometrial cancer, although the findings for serum insulin were less conclusive, with higher postchallenge levels in obese cases only (and without further adjustment for BMI) (23). All three studies excluded diabetics and examined insulin levels at various points after glucose challenge. In light of our data showing no increase in insulin secretion in endometrial cancer cases, the results of these studies may suggest that higher circulating insulin levels in cases are due to reduced hepatic insulin clearance. Alternatively, since adiposity is strongly and positively correlated with glucose and insulin levels and the cases tended to be quite heavy, one possible explanation for the insulin findings in these studies is residual confounding by adiposity.

Our findings are consistent with at least two etiologic hypotheses for endometrial cancer. The first, as noted above, is that insulin is not in the etiologic pathway, and any increase in risk noted for high insulin levels is an artifact of a positive association with

adiposity. Alternatively, BMI may mediate an effect of insulin resistance on endometrial cancer risk, as suggested by the observation that adjustment for BMI, intermediate in the pathway under this scenario, strongly attenuated the risk associated with insulin.

The strong attenuation of the association between C-peptide and endometrial cancer risk with adjustment for BMI may also be due to the relatively strong correlation between BMI and C-peptide. If BMI were measured with less random error than C-peptide, then with both variables simultaneously in the model the estimate for C-peptide might be more likely to be attenuated. In addition, BMI may represent a better measure of, for example, long-term insulin exposure, while C-peptide represents levels at one point in time.

The issue of a disease effect, namely that the tumor has itself altered the measurement of interest, is always of concern in cross-sectional studies using biologic markers. There are no prospective data to address this issue directly. This type of bias, however, is less of a concern in studies of endometrial cancer because it is one of the most benign and least extensive tumors. Furthermore, in this study, most of the cases were diagnosed with early-stage disease (116/165 with stage 1; 32/165 with stage 2; 14/165 with stage 3; 3/165 unclassified).

Another methodological concern is the appropriateness of the two control groups. Both groups were suitable for a hospital-based case series because they were at risk for the disease and were otherwise eligible to be cases. The hysterectomy controls were chosen for several reasons. One was to sample from the population that gave rise to cases that would attend these hospitals. Because hysterectomy is a simple and common procedure, the hospital-based controls were chosen to ensure some comparability in women referred to specialized hospitals for a hysterectomy. There was some concern that referred cases might have a higher prevalence of morbid obesity. By choosing referred controls, the authors attempted to minimize this bias. Another reason hysterectomy controls were included was to increase response rates to the interview and blood components of the study. The risk estimates for C-peptide were similar when calculated separately for the two control groups, with a slight difference that may have arisen by chance given the small numbers of hysterectomy controls.

Finally, this analysis was based on a subset of the entire study population. This was due to lower response to the blood component than to the interview component of the study, although the response rates were similar to or better than those of other studies collecting biologic specimens. The exclusions that further reduced the subjects for analysis, such as menopausal status, recent use of exogenous estrogens, and a history of diabetes, were used to address potential confounding and simplify the interpretation of the findings. These exclusions should act only to reduce the generalizability of our findings since they were applied equally to cases and controls. It is reassuring that the risk estimates for the major risk factors for endometrial cancer demonstrated in the entire study population are generally similar to those observed in this subset.

In summary, we observed an increased risk of endometrial cancer among women with high levels of C-peptide that was reduced after adjustment for BMI. In contrast, adjustment for C-peptide did not influence the positive association between BMI and endometrial cancer risk, suggesting that the effect of obesity on endometrial cancer risk is not mediated through high insulin levels.

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REFERENCES

1. Brinton LA, Hoover RN. Epidemiology of gynecologic cancers. In: Hoskins WJ, Perez CA, Young RC, eds. Gynecologic oncology: principles and practice. Philadelphia, PA: J. B. Lippincott Co., 1992:3–16.
2. Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr 1987;45:277–82.
3. MacDonald PC, Siiteri PK. The relationship between the extraglandular production of estrone and the occurrence of endometrial neoplasia. Gynecol Oncol 1974;2:259–63.
4. MacDonald PC, Edman CD, Hemsell DL, et al. Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. Am J Obstet Gynecol 1978;130:448–55.
5. Potischman N, Hoover RN, Brinton LA, et al. A case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst 1996;88:1127–35.

6. Austin H, Austin JM, Partridge EE, et al. Endometrial cancer, obesity and body fat distribution. Cancer Res 1991;51: 568–72.
7. Kaplan NM. The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 1989;149:1514–20.
8. Peiris AN, Sothmann MS, Hennes MI, et al. Relative contribution of obesity and body fat distribution to alterations in glucose insulin homeostasis: predictive values of selected indices in premenopausal women. Am J Clin Nutr 1989;49: 758–64.
9. Seidell JC, Cigolini M, Deurenberg P, et al. Fat distribution, androgens, and metabolism in nonobese women. Am J Clin Nutr 1989;50:269–73.
10. Swanson CA, Potischman N, Wilbanks GD, et al. Relation of endometrial cancer risk to past and contemporary body size and fat distribution. Cancer Epidemiol Biomarkers Prev 1993; 2:321–7.
11. Sturgeon SR, Brinton LA, Berman ML, et al. Past and present physical activity and endometrial cancer risk. Br J Cancer 1993;68:584–9.
12. Parker DR, Weiss ST, Troisi R, et al. Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations: the Normative Aging Study. Am J Clin Nutr 1993;58:129–36.
13. Krotkiewski M, Mandroukas K, Sjostrom L, et al. Effects of long-term physical training on body fat, metabolism and blood pressure in obesity. Metabolism 1979;28:650–8.
14. Nagamani M, Hannigan EV, Van Dinh T, et al. Hyperinsulinemia and stromal luteinization of the ovaries in postmenopausal women with endometrial cancer. J Clin Endocrinol Metab 1988;67:144–8.
15. Rutanen E-M, Stenman S, Blum W, et al. Relationship between carbohydrate metabolism and serum insulin-like growth factor system in postmenopausal women: comparison of endometrial cancer patients with healthy controls. J Clin Endocrinol Metab 1993;77:199–204.
16. Brinton LA, Berman ML, Mortel R, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol 1992; 167:1317–25.
17. Swanson CA, Potischman NP, Wilbanks GD, et al. Relation of endometrial cancer risk to past and contemporary body size and body fat distribution. Cancer Epidemiol Biomarkers Prev 1993;2:321–7.
18. Schwartz SM, Thomas DB. The World Health Organization collaborative study of neoplasia and steroid contraception. Cancer 1989;64:2487–92.
19. Potischman N, Falk RT, Laiming VA, et al. Reproducibility of laboratory assays for steroid hormones and sex hormone-binding globulin. Cancer Res 1994;54:5363–7.
20. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publication no.32).
21. Polonsky KS, Rubenstein AH. C-peptide as a measure of the secretion and hepatic extraction of insulin. Pitfalls and limitations. Diabetes 1984;33:486–94.
22. Nestler JE. Editorial: sex hormone-binding globulin: a marker for hyperinsulinemia and/or insulin resistance? J Clin Endocrinol Metab 1993;76:273–4.
23. Brown R. Carbohydrate metabolism in patients with endometrial carcinoma. J Obstet Gynecol Br Commonwealth 1974; 81:940–6.